

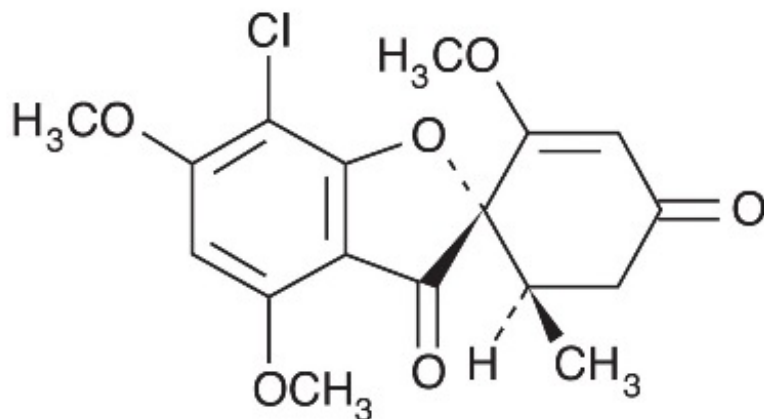
GRISEOFULVIN- griseofulvin tablet
Rising Pharmaceuticals Inc.

GRISEOFULVIN TABLETS, USP (MICROSIZE) Rx Only

Prescribing Information

DESCRIPTION

Griseofulvin microsize contains griseofulvin microsize for oral administration. The active ingredient, griseofulvin, is a fungistatic antibiotic derived from a species of *Penicillium*. The chemical name of griseofulvin is 7-chloro-2',4,6-trimethoxy-6'β-methylspiro[benzofuran-2(3H),1'-[2]cyclohexane]-3-4'-dione. Its structural formula is:



$C_{17}H_{17}ClO_6$ M.W = 352.77

Griseofulvin occurs as a white to creamy white, bitter tasting powder which is very slightly soluble in water and sparingly soluble in alcohol. Griseofulvin microsize contains particles of approximately 2 to 4 μm in diameter.

Griseofulvin Tablets, USP (microsize) 500 mg are white, capsule shaped, bisected tablets, debossed with 'Σ' and '12' on either side of the bisection and plain on the other side. Each Griseofulvin Tablet, USP (microsize) 500 mg contains 500 mg of griseofulvin microsize, and also contains corn starch, povidone, polyethylene glycol 400, polyethylene glycol 8000, lactose monohydrate, croscopovidone, silicon dioxide and magnesium stearate.

Meets USP Dissolution Test 2.

CLINICAL PHARMACOLOGY

Griseofulvin absorption from the gastrointestinal tract varies considerably among individuals mainly because of insolubility of the drug in aqueous media of the upper GI tract. Drug absorption has been estimated to range between 27 and 72%. After an oral dose, griseofulvin is primarily absorbed from the duodenum with some absorption occurring from jejunum and ileum. The peak serum level in fasting adults given 0.5 g of griseofulvin microsize occurs at about four hours and ranges between 0.5 to 2 mcg/mL. The serum level may be increased by giving the drug with a meal with a high fat content. In one study in pediatric patients 19 months to 11 years of age, 10 mg/kg of griseofulvin microsize given with milk resulted in mean peak serum concentrations approximately four-fold greater than the same griseofulvin dose given alone (1.29 mcg/mL versus 0.34 mcg/mL, respectively). Also, the area under the curve value was ten-fold larger when 10 mg/kg griseofulvin and milk were administered simultaneously as compared to the same dosage given to fasting patients. In addition, griseofulvin administered with milk resulted in more consistently detected serum levels across subjects.

Following oral administration, griseofulvin is deposited in the keratin precursor cells and has a greater affinity for diseased tissue. The drug is tightly bound to the new keratin which becomes highly resistant to fungal invasions. When the drug is discontinued, griseofulvin concentrations in the skin decline less rapidly than those in plasma.

Griseofulvin is metabolized by the liver to 6-desmethylgriseofulvin and its glucuronide conjugate.

Griseofulvin has a variable elimination half-life in plasma (9 to 24 hours). Approximately 30% of a single oral dose of griseofulvin is excreted in the urine within 24 hours and about 50% of the dose is excreted in the urine within 5 days, mostly in the form of metabolites. Unchanged griseofulvin in the urine accounts for less than 1% of the administered dose. In addition, approximately one-third of a single dose of griseofulvin is excreted in feces within 5 days. Griseofulvin is also excreted in perspiration.

Microbiology

Mechanism of Action:

The mechanism of Griseofulvin consists of binding microtubular proteins, which are required for mitosis.

Activity *In Vivo*:

Griseofulvin may be active against most strains of the following dermatophytes as described in the **INDICATIONS AND USAGE** section:

Epidermophyton floccosum, *Microsporum audouinii*, *Microsporum canis*, *Microsporum gypseum*, *Trichophyton crateriformis*, *Trichophyton gallinae*, *Trichophyton interdigitalis*, *Trichophyton megnini*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton sulphureum*, *Trichophyton schoenleinii*, *Trichophyton tonsurans*, and *Trichophyton verrucosum*.

It has no effect on bacteria or on other genera of fungi.

Activity *In Vitro*:

In vitro, griseofulvin has been shown to have activity against many dermatophytes, **but the clinical significance is unknown.**

Drug Resistance:

Although there have been reports of dermatophyte resistance to griseofulvin, the clinical significance is unknown.

INDICATIONS AND USAGE

Griseofulvin is indicated for the treatment of dermatophyte infections of the skin not adequately treated by topical therapy, hair and nails, namely:

Tinea corporis

Tinea pedis

Tinea cruris

Tinea barbae

Tinea capitis

Tinea unguium when caused by one or more of the following species of fungi:

Epidermophyton floccosum

Microsporum audouinii

Microsporum canis

Microsporum gypseum

Trichophyton crateriform

Trichophyton gallinae

Trichophyton interdigitalis

Trichophyton megnini

Trichophyton mentagrophytes

Trichophyton rubrum

Trichophyton schoenleini

Trichophyton sulphureum

Trichophyton tonsurans

Trichophyton verrucosum

Note: Prior to therapy, a dermatophyte should be identified as responsible for the infection.

Prior to initiating treatment, appropriate specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis.

Griseofulvin is not effective in the following:

Bacterial infections

Candidiasis (Moniliasis)

Histoplasmosis

Actinomycosis

Sporotrichosis

Chromoblastomycosis

Coccidioidomycosis

North American Blastomycosis

Cryptococcosis (Torulosis)

Tinea versicolor

Nocardiosis

The use of this drug is not justified in minor or trivial dermatophyte infections which will respond to topical agents alone.

CONTRAINDICATIONS

Griseofulvin is contraindicated in patients with porphyria or hepatocellular failure, and in individuals with a history of hypersensitivity to griseofulvin.

Griseofulvin may cause fetal harm when administered to a pregnant woman. Two published cases of conjoined twins have been reported in patients taking griseofulvin during the first trimester of pregnancy, therefore, griseofulvin is contraindicated in women who are or may become pregnant during treatment. Women taking estrogen-containing oral contraceptives may be at increased risk of becoming pregnant while on griseofulvin (see also **PRECAUTIONS, Drug Interactions**). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Although no direct causal relationship has been

established, spontaneous abortion has been reported rarely coincident with the use of griseofulvin.

Note: The Maximum Recommended Human Dose (MRHD) was set at 500 mg/day for the multiple of human exposure calculations performed in this label. If higher doses than 500 mg/day were used clinically, then the multiple of human exposure would be correspondingly reduced for that dose. For example, if a 1000 mg/day dose was administered to an individual, then the multiple of human exposure would be reduced by a factor of 2.

Griseofulvin has been shown to be embryotoxic and teratogenic in pregnant rats when given at a daily oral dose of 250 mg/kg/day [4X the Maximum Recommended Human Dose (MRHD) based on a Body Surface Area (BSA)]. Griseofulvin also has been shown to be embryotoxic and teratogenic in pregnant cats treated weekly with griseofulvin at doses of 500 to 1000 mg/week. There are reports of teratogenicity in a Golden Retriever when doses of 750 mg/day [1.2X the MRHD based on BSA] were administered for four weeks prior to and throughout the pregnancy, and in a study in which beagles were administered 35 mg/kg/day [1.9X the MRHD based on BSA] for intervals from one week up to the entire gestation period. Teratogenicity was also seen in mice when griseofulvin was administered in doses equivalent to 5g/kg/day [40X the MRHD based on BSA] for 2 consecutive days at various stages of the pregnancy.

WARNINGS

Prophylactic Usage

Safety and efficacy of griseofulvin for prophylaxis of fungal infections have not been established.

Serious Skin Reactions

Severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis) and erythema multiforme have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. If severe skin reactions occur, griseofulvin should be discontinued (see ADVERSE REACTIONS section).

Hepatotoxicity

Elevations in AST, ALT, bilirubin, and jaundice have been reported with griseofulvin use. These reactions may be serious and may result in hospitalization or death. Patients should be monitored for hepatic adverse events and discontinuation of griseofulvin considered if warranted (see ADVERSE REACTIONS section).

PRECAUTIONS

General

Patients on prolonged therapy with any potent medication should be under close observation. Periodic monitoring of organ system function, including renal, hepatic and hematopoietic, should be done.

Since griseofulvin is derived from species of penicillin, the possibility of cross sensitivity with penicillin exists; however, known penicillin-sensitive patients have been treated without difficulty.

Lupus erythematosus, lupus-like syndromes or exacerbations of existing lupus erythematosus have been reported in patients receiving griseofulvin.

Since a photosensitivity reaction is occasionally associated with griseofulvin therapy, patients should be warned to avoid exposure to intense or prolonged natural or artificial sunlight.

Drug Interactions:

Griseofulvin has been reported in the literature to interfere with the metabolism of various compounds. Whether this is due to a P-450 mediated enzyme induction effects on sulfurtransferase and/or glucotransferase activity, or some other mechanism is unknown.

Griseofulvin decreases the activity of warfarin-type anticoagulants, so that patients receiving these drugs concomitantly may require dosage adjustment of the anticoagulant during and after griseofulvin therapy.

Griseofulvin may enhance the hepatic metabolism of estrogens, including the estrogen component of oral contraceptives, thereby reducing the effectiveness of contraception and causing menstrual irregularities. Therefore, an alternate or second form of birth control may be indicated during periods of concurrent use (see also **CONTRAINDICATIONS**).

Cyclosporine levels may be reduced when administered concomitantly with griseofulvin, resulting in a decrease in the pharmacologic effects of cyclosporine.

Serum salicylate concentrations may be decreased when griseofulvin is given concomitantly with salicylates.

Barbiturates usually depress griseofulvin activity by decreasing plasma levels and concomitant administration may require a dosage adjustment of the antifungal agent.

Nausea, vomiting, flushing, tachycardia, and severe hypotension have been reported following alcohol ingestion during griseofulvin therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In subacute toxicity studies, orally administered griseofulvin produced hepatocellular necrosis in mice, but this has not been seen in other species. Chronic feeding of griseofulvin, at levels ranging from 0.5 to 2.5% of the diet, resulted in the development of liver tumors in several strains of mice, particularly in males. Smaller particle sizes resulted in an enhanced effect. Lower oral-dosage levels have not been tested. Subcutaneous administration of relatively small doses of griseofulvin once a week during the first three weeks of life has also been reported to induce hepatomata in mice. Thyroid tumors, mostly adenomas but some carcinomas, have been reported in male rats receiving griseofulvin at levels of 2.0%, 1.0% and 0.2% of the diet, and in female rats receiving the two higher dose levels. Studies in other animal species were inadequate assessments of tumorigenicity.

Disturbances in porphyrin metabolism have been reported in griseofulvin-treated laboratory animals. Griseofulvin has been reported to have a colchicine-like effect on mitosis and was cocarcinogenic with methylcholanthrene in cutaneous tumor induction in laboratory animals. Griseofulvin interferes with chromosomal distribution during cell division, causing aneuploidy in plant and mammalian cells. These effects have been demonstrated *in vitro* at concentrations that may be achieved in the serum with the recommended therapeutic dosage.

Suppression of spermatogenesis has been reported to occur in rats and sperm abnormalities have been observed in griseofulvin treated mice, but these were not detected in man. Male patients should wait at least six months after completing griseofulvin therapy before fathering a child.

Pregnancy: Teratogenic Effects: Pregnancy Category X: See CONTRAINDICATIONS and PRECAUTIONS, Drug Interactions.

Nursing Mothers

It is not known if griseofulvin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for griseofulvin in animal studies (see **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients 2 years of age and younger have not been established. Safety in pediatric patients older than 2 years of age at dosages greater than 10 mg/kg daily has not been established.

ADVERSE REACTIONS

There have been post-marketing reports of severe skin and hepatic adverse events associated with griseofulvin use (see WARNINGS section).

When adverse reactions occur, they are most commonly of the hypersensitivity type such as skin rashes, urticaria, and rarely, angioneurotic edema, and erythema multiforme. These may necessitate withdrawal of therapy and appropriate countermeasures. Peripheral neuropathy and paresthesias of the hands and feet have been reported and may be related to treatment duration. Most patients treated with griseofulvin for less than six months experienced improvement or resolution of their neuropathy upon withdrawal of the griseofulvin. Other side effects reported occasionally are oral thrush, nausea, vomiting, epigastric distress, diarrhea, headache, fatigue, dizziness, insomnia, mental confusion and impairment of performance of routine activities.

Proteinuria, nephrosis (sometimes associated with existing systemic lupus erythematosus), leukopenia, coagulopathy, hepatitis, elevated liver enzymes, hyperbilirubinemia, and GI bleeding have been reported rarely. Administration of the drug should be discontinued if granulocytopenia occurs.

To report **SUSPECTED ADVERSE REACTIONS**, contact Rising Pharmaceuticals at 1-866-562-4597 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

There is limited experience on overdose with griseofulvin. In case of overdose, discontinue medication, treat symptomatically and institute supportive measures as required.

DOSAGE AND ADMINISTRATION

Accurate diagnosis of the infecting organism is essential. Identification should be made either by direct microscopic examination of a mounting of infected tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Medication must be continued until the infecting organism is completely eradicated as indicated by appropriate clinical or laboratory examination. Representative treatment periods are tinea capitis, 4 to 6 weeks; tinea corporis, 2 to 4 weeks; tinea pedis, 4 to 8 weeks; tinea unguium – depending on rate of growth – fingernails, at least 4 months; toenails, at least 6 months.

General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis. In some forms of tinea pedis, yeasts and bacteria may be involved as well as dermatophytes. Griseofulvin will not eradicate these associated bacterial or yeast infections.

ADULTS: 0.5 g daily (125 mg q.i.d., 250 mg b.i.d., or 500 mg/day). Patients with less severe or 300 extensive infections may require less, whereas those with widespread lesions may require a starting dose of 0.75 g to 1 g/day. This may be reduced gradually to 0.5 g or less after a response has been noted. In all cases, the dosage should be individualized.

PEDIATRIC PATIENTS (older than 2 years): A dosage of 10 mg/kg daily is usually adequate (pediatric patients from 30 to 50 lb, 125 mg to 250 mg daily; pediatric patients over 50 lb, 250 mg to 500 mg daily, in divided doses). Dosage should be individualized, as with adults. Clinical relapse will occur if the medication is not continued until the infecting organism is eradicated.

Safety is not established at higher doses than recommended.

HOW SUPPLIED

Griseofulvin Tablets, USP (microsize) 500 mg are white, capsule shaped, bisected tablets, debossed

with 'Σ' and '12' on either side of the bisection and plain on the other side, and supplied in bottles of 30s (NDC 64980-186-03) and 100s (NDC 64980-186-01).

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Rx ONLY

Manufactured for:

Rising Pharmaceuticals, Inc.

Allendale, NJ 07401



Manufactured by:

Sigmapharm Laboratories, LLC

Bensalem, PA 19020

OS012-05 REV.0216

GRISEOFULVIN TABLETS, USP (MICROSIZE) 500 MG - 100 TABLET CONTAINER LABEL

The image shows a detailed container label for Griseofulvin Tablets, USP (microsize) 500 mg. The label is rectangular with a light blue background and a yellow curved section at the bottom right. It includes the Rising Pharmaceuticals logo, NDC number 64980-186-01, and the product name "Griseofulvin Tablets, USP (microsize)" in large bold letters. Below the product name, it says "500 mg" in a blue box and "100 Tablets" in a blue box. A yellow box with "Rx only" is also present. The label contains detailed dosage instructions for adults and children, a warning about household use, and information about the tablets' appearance (white, capsule shaped, bisected). It also includes storage instructions, a pharmacist warning, and manufacturer information for both Rising Pharmaceuticals, Inc. and Sigmapharm Laboratories, LLC. A barcode is located on the right side of the label, with the numbers "N 3 64980 18601 8" printed below it. The lot number "L032.03-R0912" is printed below the barcode. The label also includes fields for "Lot No.:" and "Exp.:". The SigmaPharm logo is in the top right corner.

Griseofulvin Tablets, USP (microsize) 500 mg Container Label

Rising Pharmaceuticals, Inc.

NDC 64980-186-01

Griseofulvin Tablets, USP (microsize)

500 mg

100 Tablets

Rx Only

GRISEOFULVIN TABLETS, USP (MICROSIZE) 500 MG - 30 TABLET CONTAINER LABEL

 **NDC 64980-186-03**

Griseofulvin Tablets, USP (microsize)

500 mg

30 Tablets

Rx only

Usual Adult Dosage: One tablet (500 mg) daily.

Usual Children's Dosage: One half to one tablet (250 mg to 500 mg) daily depending on age and weight.

For information for use, see accompanying product literature. **Not intended for household use. Dispense in a tight container as defined in the USP.**

White, capsule shaped, bisected tablets, debossed with 'Σ' and '12' on either side of the bisecting and plain on the other side.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Pharmacist: Do not use if foil seal is removed or damaged. Return to place of purchase.

Manufactured for:
Rising Pharmaceuticals, Inc.
Allendale, NJ 07401

Manufactured by:
Sigmapharm Laboratories, LLC
Bensalem, PA 19020
L090.01-R0915


N 3 64980 18603 2

Lot No.:

Exp.:



Griseofulvin Tablets, USP (microsize) 500 mg Container Label

Rising Pharmaceuticals, Inc.

NDC 64980-186-03

Griseofulvin Tablets, USP (microsize)

500 mg

30 Tablets

Rx Only

GRISEOFULVIN			
griseofulvin tablet			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:64980-186
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
GRISEOFULVIN (UNII: 32HRV3E3D5) (GRISEOFULVIN - UNII:32HRV3E3D5)		GRISEOFULVIN	500 mg
Inactive Ingredients			
Ingredient Name			Strength
STARCH, CORN (UNII: O8232NY3SJ)			
POVIDONE (UNII: FZ989GH94E)			
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)			
POLYETHYLENE GLYCOL 8000 (UNII: Q662QK8M3B)			
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)			
CROSPVIDONE (UNII: 68401960MK)			
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)			
MAGNESIUM STEARATE (UNII: 70097M6I30)			

Product Characteristics

Color	white	Score	2 pieces
Shape	CAPSULE (white, capsule shaped, bisected tablets)	Size	17mm
Flavor		Imprint Code	;12
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64980-186-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	12/06/2012	
2	NDC:64980-186-03	30 in 1 BOTTLE; Type 0: Not a Combination Product	07/01/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202482	12/06/2012	

Labeler - Rising Pharmaceuticals Inc. (041241766)

Registrant - Sigmapharm Laboratories, LLC (556234636)

Establishment

Name	Address	ID/FEI	Business Operations
Sigmapharm Laboratories, LLC		556234636	manufacture(64980-186) , analysis(64980-186)

Revised: 1/2016

Rising Pharmaceuticals Inc.